CARDIOVASCULAR MEDICINE

Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study

L Wei, J Wang, P Thompson, S Wong, A D Struthers, T M MacDonald

Heart 2002;**88**:229–233

See end of article for authors' affiliations

Correspondence to: Professor T M MacDonald, MEMO, Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; t.m.macdonald@dundee.ac.uk

Accepted 21 May 2002

Objective: To investigate patients' adherence to statin treatment prescribed following their first myocardial infarction (MI) and to estimate the effect of adherence to statins on recurrence of MI and all cause mortality.
Design: Cohort study using a record linkage database.
Setting: Tayside, Scotland, UK.
Patients: Patients who experienced their first MI between January 1990 and November 1995.
Main outcome measures: Percentage of statin use and adherence to statins by patients after an MI and the relative risk of hospitalisation for recurrent MI. The effect of adherence on all cause mortality was also examined. The covariates used were age, sex, socioeconomic deprivation, serum cholesterol concentration, diabetes mellitus, cardiovascular drug use, and other hospitalisations.
Results: Of 5590 patients who experienced an incident MI, 717 (12.8%) experienced at least one further MI. Only 7.7% of patients used statins after an MI during the study period. Compared with those not taking statins, those who had 80% or better adherence to statin treatment had an adjusted relative risk of recurrent MI of 0.19 (95% confidence interval (CI) 0.08 to 0.47) and all cause mortality of 0.47 (95% CI 0.22 to 0.99). There was no significant reduction in either end point for those who were less than 80% adherent to statins.
Conclusions: Despite the infrequent use of statin during the study period, good adherence to statin treatment was associated with lower risk of recurrent MI.

Coronary heart disease (CHD) is a leading cause of morbidity and mortality worldwide. Serum total cholesterol and low density lipoprotein cholesterol are major risk factors for recurrent cardiac events in patients following a myocardial infarction (MI). Statins (HMG CoA reductase inhibitors) are effective cholesterol lowering agents and are the drugs of choice for patients with increased cholesterol who have suffered an MI. Several large clinical trials (4S (Scandinavian simvastatin survival study), CARE (cholesterol and recurrent events), WOSCOPS (West of Scotland coronary prevention study), LIPID (long term intervention with pravastatin in ischaemic disease), and AFCAPS (Air Force coronary atherosclerosis prevention study))[1–5] on primary or secondary prevention of CHD have shown that these drugs reduce the risk of major coronary events by about 30%[6] and improve survival in patients following MI. Current guidelines recommend statin treatment when total cholesterol is $\geq$ 5 mmol/l in patients after an MI.

However, the therapeutic effect of a drug depends not only on patients having the treatment prescribed but also on their adherence or compliance with the treatment. Previous studies have shown that there is a low rate of statin prescribing and a lack of adherence to treatment by patients with CHD.[7–12]

The present study aimed at investigating the adherence to statin treatment by patients after an MI in Tayside, Scotland, and to estimate the effect of adherence on recurrence of MI and, as a secondary end point, all cause mortality.

METHODS

The study was carried out in the population of Tayside in Scotland, using the Medicine Monitoring Unit's record linkage database. This database contains several data sets including all dispensed community prescriptions, hospital discharge data, biochemistry results, and other data that are linked by a unique patient identifier, the community health number. The data collection methods for this database have previously been described.[13] These data are made anonymous for the proposes of research and the methods used are approved by the Tayside Caldicott Guardians. The project was also approved by the Tayside committee on research medical ethics.

Study population

The study population was the population of Tayside who were resident and registered with a general practitioner between January 1985 and December 1995.

Study subjects

Patients who experienced their first MI between January 1990 and November 1995 were identified from the Tayside hospital discharge data.

Study period

The study period was from January 1985 until December 1995. The first five years were used as a screening period. Subjects who had a hospitalisation for MI before 1 January 1990 were thus excluded from the study. Data were collected on each subject until 31 December 1995. The maximum follow up was thus six years.

Abbreviations: 4S, Scandinavian simvastatin survival study; AFCAPS, Air Force coronary atherosclerosis prevention study; CARE, cholesterol and recurrent events; CHD, coronary heart disease; LIPID, long-term intervention with pravastatin in ischaemic disease; MI, myocardial infarction; WOSCOPS, West of Scotland coronary prevention study

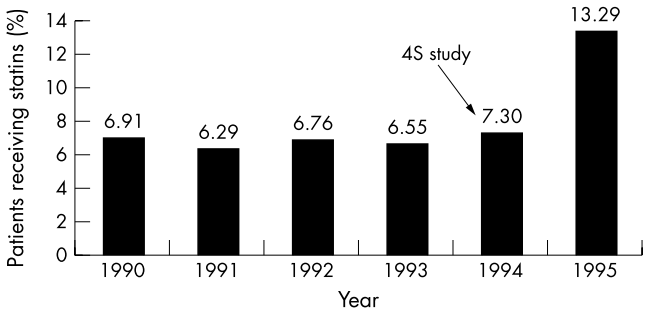

Figure 1 Percentage in each year of patients receiving statins after a myocardial infarction.

Study outcome

The primary outcome was hospitalisation for recurrent MI and the secondary outcome was death from any cause during the follow up period.

For each prescription for a statin (mainly pravastatin and simvastatin) we knew the strength of the tablet, the number of tablets dispensed, and the instructions on how these should be taken. Thus, the daily dose and the number of days treatment could be calculated. Adherence to statin treatment was calculated as the number of days with statin supply divided by the total number of days from the first prescription for a statin to the end of study. Patients with no dispensed prescribing for statins were considered to have zero adherence. If a patient collected more drug than they had been directed to use, the percentage of adherence was over 100% but we classified these subjects as having maximum adherence.

Biochemistry data

Serum cholesterol data were available for the Dundee catchment area from 1989 to December 1995, with the exception of October 1994 to April 1995.

Statistical analysis

Data were summarised as mean (SD) for continuous variables and number of subjects (percentage) for categorical variables. χ^2 and t tests were performed to determine significant differences. Cochran-Armitage trend tests were also performed if there were more than two categorical variables. The proportional hazards model was used to analyse the time to hospitalisation for recurrent MI and separately for all cause mortality, giving results in terms of risk ratios. Analyses were carried out univariately and multivariately. Multivariate analyses adjusted for age, sex, socioeconomic deprivation, lipid lowering drug treatment before MI, statin daily dose, serum total cholesterol concentration, presence of diabetes mellitus at baseline, other cardiovascular drug prescriptions,

Table 1 Characteristics of patients after a myocardial infarction (MI), Tayside, 1990–5

	MI recurrence (n=717)	No MI recurrence (n=4873)	p Value
Male (%)	412 (57.5)	2920 (59.9)	NS
Age (SD)	69.7 (11.1)	66.9 (12.2)	<0.01
Deprivation category (%)*†			
1–2 (least deprived)	180 (25.6)	1269 (27.9)	<0.05
3–4	291 (41.5)	2018 (44.4)	
5–7 (most deprived)	231 (32.9)	1256 (27.7)	
Adherence to statins (%)*			
0	693 (96.7)	4470 (91.7)	<0.01
<39	6 (0.8)	61 (1.3)	
40–79	5 (0.7)	83 (1.7)	
80–100	13 (1.8)	259 (5.3)	
Baseline cholesterol (mmol/l) (SD)‡	6.61 (1.5)	6.57 (1.4)	NS

*Test for trend between categories, p<0.01; †for 702 subjects in recurrence group and 4543 subjects in no recurrence group who had deprivation data recorded; ‡for 194 patients in recurrence group and 1279 patients in no recurrence group who had cholesterol data recorded.

Table 2 Distribution of statin use in patients after an MI by age, sex, and socioeconomic deprivation, Tayside, 1990–95

		Adherence to statins	
	Any statin use (%)	Mean (SD)	Median
Sex			
Male	158 (8.9)	73.5 (31.8)	88.3
Female	269 (7.0)	80.7 (28.4)	94.2
Age (years)*			
<50	103 (21.2)	76.3 (29.4)	89.4
50–59	152 (15.5)	75.3 (29.3)	87.8
60–69	133 (8.3)	77.3 (31.8)	93.7
70–79	33 (2.1)	78.8 (34.0)	97.7
⩾80	6 (0.6)	55.8 (45.6)	55.3
Deprivation category*†			
1–2 (least deprived)	111 (7.7),	76.3 (29.7)	89.4
3–4	153 (6.6)	74.5 (32.6)	91.2
5–7 (most deprived)	156 (10.5)	77.2 (29.7)	89.5
Death status			
Dead	28 (2.2)	65.3 (37.1)	81.4
Alive	399 (9.3)	76.9 (30.1)	90.5

*Test for trend between groups, p<0.01; †for 420 patients who had deprivation data recorded.

Table 3 Univariate and multivariate hazard ratios for recurrence of MI

	Univariate		Multivariate†	
Outcome predictor	RR	95% CI	RR	95% CI
Adherence to statins (%)				
0 (n=5163)	1.00		1.00	
<39 (n=67)	0.55	0.25 to 1.22	0.59	0.22 to 1.59
40–79 (n=88)	0.38*	0.16 to 0.90	0.51	0.19 to 1.35
80–100 (n=272)	0.35**	0.20 to 0.60	0.19**	0.08 to 0.47
Statin daily dose (high *v* 10 mg)	0.47	0.18–1.25	0.42	0.06 to 3.26
Lipid lowering drug use before MI (yes *v* no)	0.87	0.45–1.87	2.58**	1.19 to 5.60
Other lipid lowing drugs	0.45*	0.26 to 0.78	0.49	0.22 to 1.14
β Blockers	0.67*	0.57 to 0.79	0.65*	0.42 to 1.00
Antiplatelet + aspirin	0.92	0.80 to 1.07	0.93	0.58 to 1.51
Diuretics	0.92	0.80 to 1.07	0.58*	0.36 to 0.92
ACE inhibitor	0.67**	0.55 to 0.82	0.80	0.49 to 1.31
Other antihypertensive drugs	0.63	0.35 to 1.15	0.57	0.20 to 1.63
Nitrates	0.91	0.79 to 1.06	0.83	0.51 to 1.36
Calcium channel blocker	0.95	0.82 to 1.11	1.19	0.76 to 1.87
Number of types of CV drugs used				
0	1.00		1.00	
1–2	1.25	1.01 to 1.56	1.93	0.90 to 4.15
3–4	0.94	0.77 to 1.15	1.40	0.41 to 4.85
⩾5	0.63**	0.48 to 0.83	1.89	0.33 to 10.97
Sex (male *v* female)	0.88	0.76 to 1.02	1.13	0.81 to 1.56
Age (years)				
<50	1.00		1.00	
50–59	1.57*	1.06 to 2.34	1.27	0.67 to 2.38
60–69	1.94*	1.34 to 2.82	2.14*	1.17 to 3.92
70–79	2.44**	1.69 to 3.54	2.72**	1.43 to 5.17
⩾80	3.19**	2.18 to 4.67	3.99**	1.79 to 8.87
Socioeconomic deprivation				
1–2 (least deprived)	1.00		1.00	
3–4	1.01	0.84 to 1.22	1.01	0.69 to 1.49
5–7 (most deprived)	1.25*	1.03 to 1.52	1.52*	1.04 to 2.21
Baseline cholesterol	0.99	0.90 to 1.10	1.07	0.96 to 1.20
Diabetes mellitus	2.16**	1.69 to 2.76	2.16**	1.38 to 3.37
Year 1994 (after *v* before)	0.80	0.57 to 1.02	0.61	0.30 to 1.22
Other hospitalisation after MI (excluding surgical admission)	1.33	0.93 to 1.88	1.69	0.91 to 3.13

*p<0.05; **p<0.01; †for 1419 patients.
ACE, angiotensin converting enzyme; CI, confidence interval; RR, relative risk.

and other hospitalisations (excluding surgical events) during the follow up.

All statistical analyses were carried out using SAS version 8.0 (SAS Institute, Cary, North Carolina, USA).

RESULTS

There were 5590 patients who experienced their first MI between January 1990 and November 1995. Of these patients, 717 (12.8%) experienced at least one further MI and 1299 (23.2%) died during the follow up period. Only 427 (7.7%) of all patients who had an MI received statins following discharge. The average follow up of the study was 2.4 years. There was a significant increase in statin use after the 4S results were published in 1994 (fig 1). Among patients who were taking statin treatment, 63.7% had greater than 80% adherence.

Table 1 shows the characteristics of the patients with recurrent MI and those free from MI recurrence. There were significant differences in age, social deprivation category, and adherence to statins between the two groups. Patients in the recurrent MI group were older, more deprived, and less likely to be taking statin treatment than those in the group free from MI recurrence. No significant differences in sex and serum cholesterol concentration at baseline were found between the two groups. A test for trend also showed that there was a significant difference in deprivation category and adherence to statin treatment between the two groups. Similar results were found between the dead and alive patient groups.

Table 2 details the statin use and adherence to statin treatment by age, sex, deprivation category, and death status. Older patients were less likely to be prescribed statins than young patients. Women tended to have better adherence to statin treatment than men but there was no significant difference in statin prescribing between sexes. Overall patients living in more deprived areas had the highest prescribing of statins and

Table 4 Univariate and multivariate hazard ratios for all cause mortality

	Univariate		Multivariate†	
Outcome predictor	RR	95% CI	RR	95% CI
Adherence to statins (%)				
0 (n=5163)	1.00		1.00	
<39 (n=67)	0.45*	0.23 to 0.87	0.94	0.39 to 2.27
40–79 (n=88)	0.22**	0.09 to 0.51	1.15	0.44 to 3.00
80–100 (n=272)	0.22**	0.13 to 0.37	0.47*	0.22 to 0.99

*p<0.05; **p<0.011; †for 1419 patients.

there was a significant trend between statin use and deprivation category. However, there was no correlation between statin adherence and deprivation.

Table 3 shows the results of both univariate and multivariate Cox regression analysis for recurrence of MI. Compared with those not taking statins, only greater than 80% adherence to statins was significantly associated with a lower risk of recurrent MI in the multivariate analysis. β Blocker use and diuretic use were also associated with lower risk of recurrent MI. Patients who were older, had lipid lowering drug treatment before MI, resided in deprived areas, or had diabetes mellitus at baseline had a higher risk of recurrent MI. Table 4 shows the crude and adjusted relative risks for all cause mortality in MI patients. The results are similar to the recurrent MI data, with only those subjects who had greater than 80% adherence to statin treatment having significantly lower risk of all cause mortality.

DISCUSSION

Scotland has one of the highest incidence rates of CHD in the world. Although coronary mortality has been declining in the past decade, an aging population means that the prevalence of CHD is increasing. In recent years the number of patients admitted to Scottish hospitals for treatment of CHD has increased.[14] This growing problem will be a major source of rising health care costs.

The benefits of statin treatment for the secondary prevention of MI have been well documented. The present study found that only 7.7% of patients after an MI were taking statin treatment but at the time these data were collected the evidence base was not strong. There was a major influence on prescribing of statin for secondary prevention after the 4S results were published. Between 1994 and 1995 statin use almost doubled.

We may have underestimated the intention to treat with statins in the present study, as adherence to treatment was based on the dispensing of prescriptions after discharge from hospital. Thus, we could not distinguish between people who were not adherent to prescriptions that were written but were not redeemed at pharmacies, people who had prescriptions that were written but not collected from the practice, and people who were never prescribed statins.

Poor adherence to statin treatment may explain a poor outcome of patients with CHD. The adherence goal of 80% of prescribed dose is used conventionally in clinical trials of safety and efficacy that have been used to support a new drug registration. Adherence to statin treatment prescribed outside of clinical trials is poor.[15] However, in our study, 69% patients aged over 65 years had greater than 80% adherence. This was a higher proportion than that found by Avorn and colleagues.[16] Another study of adherence found that only 37% of participants adhered to their lipid lowering regimens throughout a two year study period (defined as taking at least 90% of all doses).[17]

In the present study, women were more likely to adhere to statin treatment than men but statins were less frequently prescribed to women than men. High prescribing rates were found in patients who were living in the more deprived areas. After publication of the 4S results, the increase in prescriptions in Tayside was confined mainly to socially deprived patients, as in other areas.[7 18] However, deprivation was not associated with adherence in our study while another study in the USA showed that lower socioeconomic status was linked to lower adherence.[16] This may be explained by different population characteristics, prescribing habits, or health care systems.

There are several means available for measuring adherence to drug treatment. The most commonly used method is a self reported questionnaire. Pill counts and self recorded diaries of medication taking are less frequently used. Electronic devices that record the opening of containers are also available but used infrequently. A surrogate for adherence measurement is the therapeutic response of lowered serum low density lipoprotein cholesterol concentration.

Over the past decade record linkage has become an efficient method for measuring adherence to drug treatment in large population studies. Unlike clinical trials, which focused mainly on men (81–100% men) and the young (mean age 55–59 years),[19] population based record linkage studies allow real world populations to be studied. In our study 40.4% of the patients were women.

We assumed that if a prescription was filled then patients would adhere to treatment but we had no way of knowing whether patients actually took the pills. However, this problem is not unique and in fact applies to the vast majority of studies including randomised controlled trials.

Our study showed that good adherence to statin treatment was significantly associated with lower risk of further MI. After adjusting for prior lipid lowering drug treatment (probably a marker of severe or familial hyperlipidaemia), statin daily dose, and other risk factors, only patients with ⩾ 80% adherence to statin treatment had significantly lower risks of further MI and of all cause mortality. Although smoking information (one of the main risks of CHD) was not available for the study, we used socioeconomic deprivation score as a surrogate for this as the Scottish health statistics data showed that there was a significant correlation between smoking and social class.[20] β Blocker use, diuretic use, and lack of socioeconomic deprivation were associated with lower risk of recurrent MI, as others have found.[21 22] Patients who were older, had lipid lowering drug treatment before their MI, and had diabetes mellitus at baseline were associated with higher risk of recurrent MI. These findings help validate our dataset, as we found what might be expected with these other risk factors.

Conclusions

Despite the infrequent use of statins during the study period, good adherence to statin treatment was associated with lower risk of recurrent MI.

ACKNOWLEDGEMENTS

MEMO is part of the MRC Health Services Research Collaboration. L Wei was supported by an unrestricted fellowship from Pharmacia Ltd.

Authors' affiliations

L Wei, J Wang, P Thompson, S Wong, A D Struthers, T M MacDonald, Medicines Monitoring Unit, Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee, UK

REFERENCES

1 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;**344**:1383–9.
2 **Sacks FM**, Pfeffer MA, Moye LA, *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events trial investigators. *N Engl J Med* 1996;**335**:1001–9.
3 **Shepherd J**, Cobbe SM, Ford I, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland coronary prevention study group. *N Engl J Med* 1995;**333**:1301–7.
4 **The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group**. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–57.
5 **Downs JR**, Clearfield M, Weis S, *et al*. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas coronary atherosclerosis prevention study. *JAMA* 1998;**279**:1615–22.
6 **Maron DJ**, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;**101**:207–13.

7 **Miller M**, Byington R, Hunninghake D, *et al*. Sex bias and underutilization of lipid-lowering therapy in patients with coronary artery disease at academic medical centers in the United States and Canada. Prospective randomized evaluation of the vascular effects of Norvasc trial (PREVENT) investigators. *Arch Intern Med* 2000;**160**:343–7.
8 **Fonarow GC**, French WJ, Parsons LS, *et al*. Use of lipid-lowering medications at discharge in patients with acute myocardial infarction: data from the national registry of myocardial infarction 3. *Circulation* 2001;**103**:38–44.
9 **McBride P**, Schrott HG, Plane MB, *et al*. Primary care practice adherence to national cholesterol education program guidelines for patients with coronary heart disease. *Arch Intern Med* 1998;**158**:1238–44.
10 **Andrade SE**, Walker AM, Gottlieb LK, *et al*. Discontinuation of antihyperlipidemic drugs: do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med* 1995;**332**:1125–31.
11 **Insull W**. The problem of compliance to cholesterol altering therapy. *J Intern Med* 1997;**241**:317–25.
12 **LaRosa JH**, LaRosa JC. Enhancing drug compliance in lipid-lowering treatment. *Arch Fam Med* 2000;**9**:1169–75.
13 **Evans JMM**, MacDonald TM. The Tayside Medicines Monitoring Unit (MEMO). In: Strom BL, ed. *Pharmacoepidemiology*, 3rd edn. Chichester: Wiley, 2000:361–74.
14 **Scottish Health Survey 2000**. Section C8: heart disease. Edinburgh: Information and Statistics Division 2001;C8:1.
15 **Tsuyuki RT**, Bungard TJ. Poor adherence with hypolipidemic drugs: a lost opportunity. *Pharmacotherapy* 2001;**21**:576–82.
16 **Avorn J**, Monette J, Lacour A, *et al*. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA* 1998;**279**:1458–62.
17 **Sung JC**, Nichol MB, Venturini F, *et al*. Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. *Am J Manag Care* 1998;**4**:1421–30.
18 **Packham C**, Pearson J, Robinson J, *et al*. Use of statins in general practices, 1996–8: cross sectional study. *BMJ* 2000;**320**:1583–4.
19 **LaRosa JC**, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;**282**:2340–6.
20 **Scottish Health Survey 1995**. Volume 1, chapter 4: smoking. Edinburgh: The Stationery Office 1997:140–1.
21 **Gottlieb SS**, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;**339**:489–97.
22 **MacDonald TM**, Butler R, Newton RW, *et al*. Which drugs benefit diabetic patients for secondary prevention of myocardial infarction? *Diabet Med* 1998;**15**:282–9.

IMAGES IN CARDIOLOGY

Magnetic resonance imaging of left atrial thrombus

An 83 year old man presented with left hemiplegia and atrial fibrillation. Cranial computed tomography and magnetic resonance imaging (MRI) showed cerebral infarction at the area of right middle cerebral artery. We used MRI (Signa, 1.5T, General Electric, Milwaukee, Wisconsin) for visualising the left atrial appendage (LAA). On the MRI of triple inversion recovery (IR) fast spin echo (FSE) sequence, the images of the left side of the heart are clearly seen in a long axis view. LAA is imaged on the left ventricular basal anterior wall. Mass with high signal intensity in the LAA is visible and distinctive from the LAA wall (below left). Anticoagulant treatment was initiated, and aphagia and dysarthria improved after four days of warfarin. The thrombus in the LAA was confirmed by transoesophageal echocardiography (TOE) and its size was observed to be relatively small. The MRI was repeated and the LAA thrombus disappeared (below right).

Although TOE is well established as the method for evaluation of LAA thrombi, this method is semi-invasive and cannot be used at the acute phase of cerebral infarction. Black blood technique is used to evaluate cardiac anatomy, and triple IR FSE sequence can be used to reduce more blood signal and related artefacts including fat. In our case, LAA thrombus could be detected by using this method without gadolinium injection. The non-invasive nature and safety of MRI makes it ideal for serial follow up of thrombi in LAA, even in acute cerebral infarction with a complication of aphagia or dysarthria.

H Ohyama
K Mizushige
N Hosomi
katsumz@kms.ac.jp